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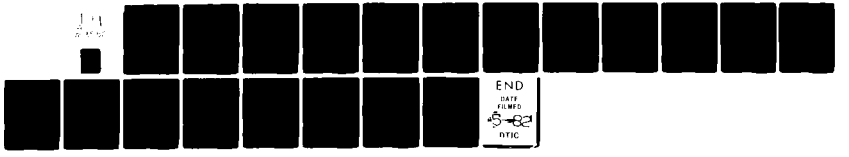

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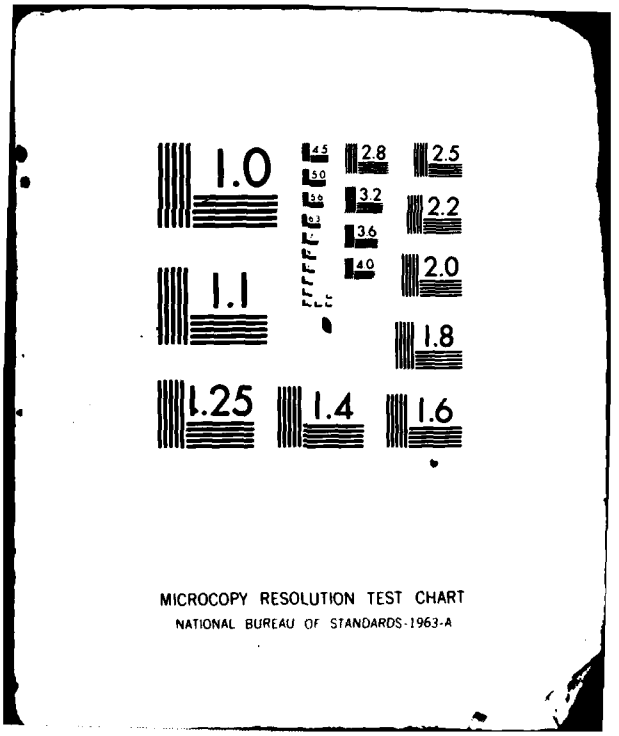
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FINAL REPORT

to the

OFFICE OF NAVAL RESEARCH

for

Contract N00014-75-C-0132
November 1974 - June 1980

SUBJECT:
Brain and Adrenal Metabolic Responses to Stress
(The Role of Brain Catecholamines in Regulation of Response to Stress)

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March 15, 1982

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The results of this contract exceeded our fondest hopes. The contract, dealing with brain metabolism and brain and adrenal responses to stress was highly productive scientifically and produced basic information that is clearly relevant to an understanding of basic stress mechanisms. Concerned with the ways in which stress might alter the neurochemistry of the brain a broad series of investigations were initiated and completed.

The studies centered about the catecholamine neurotransmitters. Catecholamines, including dopamine, norepinephrine, and epinephrine in the brain, are known to be extremely important in the response to stress. All three of these amines are important in times of stress. Indeed, the differential role of neurotransmitters in stress was first found by the principal investigator and work dealing with epinephrine in brain, sponsored in part by the ONR, received the A. E. Bennett Award.

In the phases of the work supported by this contract investigation was undertaken in several different but related areas. These included studies of specific stresses including fighting stress, cold water swimming stress, drug induced stress, and isolation stress. Investigations were conducted of the genetic differences in the ability to form the catecholamines and of the genetic factors in the aggressive behavior. The adrenal gland was studied in stress states with the finding that there were delayed effects of cold stress on key enzymes effecting the ability to form adrenaline. The enzyme forming epinephrine in human brain was characterized and studied. Of great importance was a set of studies which resulted in the first purification from brain tissue of the enzyme tyrosine hydroxylase, the controlling step in the formation of catecholamines and an enzyme which undergoes marked changes in time of stress. Evidence was provided that the mechanism of the change in

time of stress is phosphorylation.

A series of studies were conducted of the effects of various drugs on aggressive behavior. Isolation housing was shown to alter cyclic AMP mechanisms in the brain. Social behavior was studied in relation to drugs and the effects of amphetamine in relation to paranoid behavior demonstrated using a non-human primate model. The relation of social stress to hormonal systems in humans was demonstrated as part of a study of an exciting new research area, sociophysiology.

The final phase of the work dealt with the endorphins and enkephalins in the brain, morphine-like materials which are present in human brain and blood. A series of studies were undertaken with these systems including a demonstration that the morphine-like substances interact with the brain catecholamine systems and that pain mechanisms in the human may be due in part to the endorphin systems, a process of considerable interest in times of stress.

The results of the contract, in any perspective, were gratifying. The publication record, which is included at the end of this report, speaks for itself. In addition students, including both pre-doctoral and post-doctoral persons, received training and experience related to stress mechanisms. We are very pleased with the new knowledge which was developed by this contract and by the work which followed it through our Selected Research Opportunity Award, SRO-001.

We found the ONR staff with whom we worked extremely helpful, knowledgeable, straightfoward and encouraging. Dr. Donald Woodward was particularly important to our efforts. The staff monitoring and interaction greatly facilitated the work of the contract.

A few of the studies resulting from the contract are described in the following materials:

Effects of a Stress on Neurotransmitters in the Brain

Brain norepinephrine metabolism and catecholamine synthesis were measured in rats subjected to electric footshock in the presence or absence of another subject. Animals shocked in pairs engaged in fighting behavior, whereas animals receiving shock without another rat present could not fight. Marked differences in the metabolism of norepinephrine formed from intracisternally injected radiolabeled dopamine were found in the two groups receiving footshock. Within each experimental group, alterations in norepinephrine metabolism showed anatomic specificity, and temporal effects on metabolism in various brain regions were observed at various intervals after presentation of footshock. The observed changes in norepinephrine metabolism suggest that, in rats receiving footshock without a partner, norepinephrine turnover in the medulla-pons specifically increases during the shock period; during the 1 hour period postshock, however, norepinephrine turnover in the medulla-pons is decreased. Radiolabled normetanephrine levels are decreased markedly at all times, suggesting that norepinephrine metabolism in the medulla-pons is primarily deaminative (via monoamine oxidase intraneuronally) in the face of the shock procedure. In contrast, rats shocked in pairs, thereby eliciting fighting responses, show no alterations in regional norepinephrine metabolism during the period of shock but have elevated norepinephrine turnover rates in both medulla-pons and diencephalon during the subsequent 1-hour period. This change is accompanied by a slight shift in metabolism toward normetanephrine. Studies of catecholamine synthesis from radiolabled tyrosine revealed no significant changes in amine formation in rats shocked alone, but norepinephrine formation in fighting rats was elevated. Furthermore, within the fighting group there was a significant positive correlation between the number of fights and the degree to which norepinephrine synthesis was increased.

Effects of Cold Stress on Transmitter Enzymes:

The activities of the adrenal enzymes tyrosine hydroxylase (TH) and phenylethanolamine-N-methyltransferase (PNMT) were found to be elevated when mice were subject to 4°C ambient temperature. Only a single hr of cold exposure is required to achieve increased activity, provided that the measurements are made 12 hr after the cold exposure is initiated. After the cold stress is terminated, PNMT activity remain elevated for 12 hr. TH demonstrates a biphasic response to cold exposure, as the enzyme activity shows a second increase 12 hr after the stress has ended. The data indicates that short periods of stress result in demonstrated biochemical changes that persist long after the stress has ended.

Isolation Environment on Brain Amines

The effects of living alone or in groups of 3 for 4 wk. on brain biogenic amine metabolism was investigated in rats. Living alone produced an increase in brain norepinephrine turnover relative to the grouped subjects. In addition, reserpine and para-chlorophenylalanine treatment affected brain norepinephrine levels more after individual housing than after group housing. Brain serotonin metabolism showed minimal changes in differentially housed rats. There findings demonstrate the powerful effect of social behavior on brain neurotransmitters.

Effects of Cold Water Stress and Hallucinogenics on Brain Amines

The effects of cold water stress were compared to LSD, psilocybin, mescaline, and amphetamine on the metabolism of tritiated norepinephrine in rat brain. Graded doses (130-1300 microg/kg) of LSD showed no specific effects on brain catecholamine metabolism, suggesting that this drug had little direct activity on brain noradrenergic neurons. Psilocybin (25 mg/kg) had effects similar to those obtained with amphetamine (2 mg/kg) as evidenced by a prominent and sustained elevation in radiolabeled normetanephrine

content. These findings are consistent with an increased release of norepinephrine from central nerve endings. Cold water swim stress, on the other hand, resulted in a profound increase in deaminated catechol metabolites, suggesting that the intracellular catabolism of norepinephrine was affected specifically. Mescaline (25 mg/kg) had a biphasic effect onbrain norepinephrine metabolism. Shortly after injection, mescaline-treated rats had a metabolite pattern similar to animals subjected to cold water swimming; from 90 minutes to 4 hours after mescaline, however, radiolabled normetanephrine levels were elevated markedly. Based on these data, mescaline appears to cause an intial increase in intracellular norepinephrine metabolism, followed by a period of enhanced release similar to the effects of amphetamine and psilocybin. The data indicate that the psychotomimetic drugs tested work by different mechanisms in terms of brain norepinephrine metabolism and demonstrate powerful effects of cold water stress on such mechanisms.

Genetic Aspects of the Synthesis of Catecholamines in the Adrenal Medulla

Although the hormones of the adrenal medulla have great importance in the response to stress, including psychological stress, few studies have investigated genetic factors related to the formation, secretion, or utilization of adrenaline and noradrenaline. The possibility of genetic variation in adrenal medullary activity is suggested by several lines of evidence. We have found that there are marked strain differences in the activity of the enzymes involvedin the synthesis of the adrenal medullary hormones within a series of inbred mouse strains. In the case of tyrosine hydroxylase, the rate-limiting step in the formation of catecholamines, differences of as much as fourfold have been found, while for phenylethanolamine N-methyltransferase, the enzyme which converts norepinephrine to epinephrine, differences of 2-5 fold have been noted.

Genetic studies of the strains provide evidence that genetic factors are very important in determining the activity of the enzymes involved in catecholamine formation. Major differences in regulatory mechanisms involving the enzymes can also be demonstrated between the strains. Such differences in the capacity to form catecholamines may have significance in the response to stress and in behavior.

Genetic Analysis of Agressive Behavior in Two Strains of Mice

It has been known for several decades that genetic factors contribute to the variation in intermale mouse agression. Marked differences have been demonstrated in the relative agressivity various inbred mouse strains and response to selection for high and for low agression has been demonstrated. Examination of BALB/cJ and A/J mouse strains revealed marked differences in their levels of isolation-induced agression. Using the dangle paradigm, we found that BALB/cJ males were uniformly aggressive, while A/J males showed no tendency to attach. Genetic analysis showed that the expression of aggressive behavior in the F_1, F_2, and backcross generation was consistent with the transmission of high agressivity as a single autosomal recessive trait. Although the data are consistent with a major locus effect, more complex polygenic modes of inheritance have not been excluded.

Tyrosine Hydroxylase: A Stress Regulatory Enzyme. First Purification from Brain.

Tyrosine hydroxylase (Th) catalyzes the initial and most probably rate-limiting step of catecholamine biosynthesis. Knowledge of the regulation of this enzyme is crucial, therefore, for an understanding of catecholamine synthesis in the adrenal gland and in the peripheral and central nervous systems. Tyrosine hydroxylase was purified from bovine corpus striatum. The purification involved sequential DEAE cellulose, hydroxylapatite and CM Sephadex C-50 chromatography, followed by glycerol density gradient

centrifugation. Final preparations appeared to be 90 to 100 per cent pure as judged by polyacrylamide gel electrophoresis under denaturing conditions in acetic acid-urea. The enzyme was estimated to have a minimum molecular weight of approximately 60,000 daltons. Purified TH could be activated *in vitro* by incubation with magnesium adenosine triphosphate and the catalytic subunit of cyclic AMP-dependent protein kinase. When the final purified preparation of TH was incubated under these conditions utilizing [γ-^{32}P]ATP, it was found to incorporate 0.7 to 0.9 mol of phosphosphorus/mol of protein. These results suggest that the activation of TH in the presence of phosphorylating conditions is due to its phosphorylation by cyclic AMP-dependent protein kinase. These results are particularly important since in times of stress the activity of tyrosine hydroxylase may be changed 6-10 fold.

Epinephrine Forming Enzyme in Human Brain

The presence of epinephrine in the brain has long been known and the enzyme, phenylethanolamine-*N*-methyltransferase (PNMT), which catalyses the conversion of norepinephrine to epinephrine in the adrenal has also been reported to be present in the brain by ourselves and others. While most of the studies on the epinephrine forming activity were done in brains of lower mammalian species, very little is known about this enzyme in the human brain. In order to learn more about the human brain enzyme, we began to study its characteristics and attempted to develop some of the methodology for obtaining purified forms of the enzyme. PNMT-like activity was found in the high speed supernatant fraction of both the hypothalamus and medulla. When phenylethanolamine was used as a substrate at 2mM final concentration, linearity was obtained up to 1.1 mg of protein. The product formation was linear up to 90 minutes. Dialysis of the supernatant increased activity by 25 percent. Phosphate buffer at pH 7.9 gave higher activity than Tris buffer at pH 8.6. Eighty-seven percent of the extracted product was volatile

contaminant, while only 5 percent was lost on evaporation from bovine adrenal preparation. Thin-layer chromatography, using 2 different solvent systems, showed that only 7 percent of the extracted, evaporated product from brain extract co-migrated with the product from adrenal enzyme. 75 to 86 percent of the extracted product from adrenal preparation was recovered on thin-layer chromotagraphy. Substrate speciificity was determined by comparing phenylethylamine or substituted phenylethylamine to their more active β-hydroxy analogues. From the determination of the apparent K_ms, norepinephrine was found to be the best substrate. The K_m for norepinephrine was 5 μM and for SAM 5 μM. High concentration of norepinephrine inhibited enzyme activity. Dithiotheitol at 0.5 mM final concentration inhibited enzyme activity by 70 percent. Enzyme activity was completely inhibted in the present of 1 mM N-ethylmaleimide, the effect of inhibition was reversed by the addition of 1 mM mercaptoethanol.

Enzyme purification was also indertaken with partial success. Low enzymatic activity, interfering substances during the assay procedure and the presence of nonspecific methyltransferase make this characterization difficult. Although substantial progress was made, further work is required in order to refine the methodology for purifying and characterizing the enzyme. By its nature PNMT in brain, responsible for the formation of brain adrenaline, is involved in a system of great significance for the response to stress.

Increase in Agression Following Antidepressent Drugs

Central catecholamine metabolism appears clearly related to various forms of animal agression. We had previously found that drugs which appear to facilitate central adrenergic metabolism, such a rubidium, appear to facilitate irritable agression in the rat. One group of drugs which clearly alter catecholamine metabolism is the antidepressants, both dibenzazepine

compounds and monoamine oxidase inhibitors. Drugs such as the dibenzazepines when used in repeated doses increase norepinephrine turnover. Since with other conditions of increased catecholamine metabolism irritable agression is increased, we posited that repeated administration of dibenzazepine compounds or MAO inhibitors could facilitate shock-induced agression in the rat. Rats were tested for changes in shock-induced fighting following treatment with antidepressants of both the dibenzazepine and monoamine oxidase inhibitor classes of drug. Rats were retested for shock-induced fighting 3, 4, and 5 days after initial injections of imipramine (10 mg/kg IP bid), amitriptyline (10 mg/kg IP bid), and desmethylimipramine (10 mg/kg IP bid), or saline. All three dibenzazepine groups showed increased levels of shock-induced fighting ($p<0.01$). In addition, rats were retested for shock-induced fighting 6, 30, 54, and 78 hours following the initiation of treatment with daily injections of saline, or the monoamine oxidase inhibitors: nialamide (100 mg/kg/day), iproniazid (150 mg/kg/day), and pargyline (20 mg/kg/day). All three monoamine oxidase inhibitor groups showed increased levels of shock-induced fighting after 30 hr ($p<0.001$). There was no difference in the jump threshold of rats treated with pargyline or saline. The results suggest the powerful effect of these agents on agressive behavior.

Alkali Metal Cations: Effects on Isolation-Induced Agression

Lithium and rubidium alter agressive behavior in animals and man. This study was carried out to observe the effect of the alkali metal cations on isolation-induced fighting in mice. Alkali metal cations were given in varying doses over 14 days to CF-1, male mice, isolated for 4 weeks prior to testing for isolation-induced fighting. Lithium and cesium in doses of 4.5 and 6.0 mel/kg reduced the duration of isolation-induced agression in a 15 min test period when compared with controls. Toxicity was evident in the cesium-treated, but not the lithium-treated mice. No enhancement of agression

was seen in the rubidium-treated group.

Taming Effects of PCPA on the Aggressive Behavior of Rats

Lesions in the septal area of the rat brain produce a septal rage syndrome characterized by excessive irritability, hyperactivity and increased aggressiveness. Septal lesions have been noted by various investigators to increase generalized irritability sensitivity to pain and shock-induced agression. This syndrome declines markedly with 2 to 3 weeks following surgery. Septal irritability is rapidly suppressed by IP injections of para-chlorophenylalanine (PCPA) within 30 min. PCPA does not affect the levels of shock-induced agression in unlesioned rats. Consequently, this study was designed to test whether a PCPA-induced attenuation of septal irritability also lowered the level of shock-induced aggression observed in rats with septal lesions, which would suggest that both types of agression might be of common etiology. We found that septal irritability and shock-induced agression were suppressed by the administration of p-chlorophenylalanine (PCPA) to septal rats. The levels of septal irritability and shock-induced fighting were significantly lower in septal, PCPA-treated rats than in nontreated septal rats. Since both parameters of septal aggression were reduced by PCPA, and while PCPA has no effect on shock-induced fighting of unlesioned rats under similar parameters, it appears that ooth forms of aggression may function through a common neural mechanism. The work suggests a septal-serotenergic system which, when functional, inhibits several forms of aggression.

Methylxanthine-Facilitated Shock-Induced Aggression in the Rat

The methylxanthines, including caffeine and aminophylline (a theophylline preparation), have a variety of chemical and behavioral effects. Since these drugs reportedly increase central catecholamine turnover and because facilitated central CA turnover has been linked by us to increases in

shock-induced aggression, this study examined whether these drugs would facilitate shock-induced aggression in the rat. The methylxanthines caffeine and aminophylline, in daily doses of 100 mg/kg, facilitated shock-induced aggression in the rat. Under the limited parameters of this study, there was no induction of mouse-killing behavior or alteration of jump thresholds. Additional studies showed the optimal dose and time course for the facilitation of shock-induced aggression by caffeine to be 50 mg/kg administered i.p. 4 h prior to testing. Facilitation of a central adrenergic system may be the mechanism of action.

Effects of Agression on Brain Cyclic AMP

Rats subjected to electric footshock display two disparate behaviors, escape-attempts or aggressive attack, depending on whether the rat is shocked alone or with a conspecific. Different responses in blood pressure, ACTH levels, and brainstem noradrenaline turnover develop in these two patterns of behavior. On the basis of these studies we hypothesised an additional differential response for brain cyclic AMP levels. We now report a 100 percent increase in whole brain cyclic AMP following shock-induced fighting but not after identical footshock given to isolated rats. This increase occurred with or without systemic pretreatment of the rats with caffeine, an inhibitor of phosphodiesterase, the enzyme which deactivates cyclic AMP. These results are in accord with other studies which have demonstrated physiological, neurohumoral, and neurochemical differences elicited by footshock when delivered to rats alone, inducing primarily attempted escape behavior (a fear response) and when delivered in the presence of a conspecific, inducing fighting behavior (an aggressive response). The large increase in cyclic AMP with fighting is consistent with the multiple associations of aggression and cyclic AMP with central catecholamine metabolism. A potential causal and temporal relationship between the increase

in cyclic AMP and increased noradrenaline turnover following fighting could be explored in future studies in the light of the increase in noradrenaline turnover following fighting observed in other aspects of our ONR supported work.

Hormone Activity and Social Behavior

Few studies have looked at hormonal or neurochemical correlates of social behavior. Some of our data suggests that in situations in which group structure emerges solely out of interaction and is not strongly mediated by the situation, epinephrine and norepinephrine orders according to the acquired rank of group members. In another study described here, a different task was used in which interactional relationships are partially imposed by the task itself. The task was an open interaction setting and required groups of three males to come to a consensus. Pre- and post-session urinary amines were taken and assayed. Scorings of group interaction were made for task acts intiated and for procedural acts, thus providing two measures of group structure on which rank of the group members could be assessed. These scorings were made from direct observation and from video tapes. Perceptions of group members as to the ranking of the group members was also taken. On task rank and on procedure rank, neither pre- nor post-session sample of epinephrine or norepinephrine was significantly related to acquired rank. However, dopamine was significantly related to procedure rank on pre-session samples and to task rank on both pre- and post-session samples. Pre-session dopamine scores were highest for those members who ranked first, next highest for those who ranked second, and lowest for those who ranked third as shown in the table. The within group data is consistent with the data aggregated by ranks across groups. Within groups, people who started with a high dopamine level were especially likely to become high rank on procedure. While dopamine levels in this study suggest ability to predict to acquired status, we have evidence

from some of our other work, also involving 3 person interaction, that the nature of the task and the form of social interaction involved may profoundly influence the results. Thus, in another study involving 3 person interaction groups without a prescribed task, prior dopamine did not predict acquired rank, in contrast to the situation here. In that study hormonal changes in the post-session sample suggested that acquired rank influenced hormonal output. Social processes profoundly influence behavior and are complex. A variety and richness of patterns is what one would expect if the hormones are mediated by and are mediators of the social structure. Despite complexities, it is becoming clear that there are ways of documenting the relationships between social and hormonal events.

An Animal Model of Paranoia: Effects of Amphetamine on Social Behaviors

Paranoia can frequently be related to apparantly inappropriate aggression. Amphetamines are related to catecholamines and to aggression and paranoia. We asked whether amphetamines will cause an increase in species-specific responses to danger in an animal when the organism is in a relatively neutral or unchanged environment and when the normal perceptual system is altered by only amphetamine. Or, more directly, does amphetamine produce an animal that behaves as if there was a threat in his environment. The results indicate that amphetamine administration caused a significant decrease in the time spent "eating" and "huddling/sleeping" for each animal during the three weeks of drug administration only. The frequency of the behaviors increase for some animals, but was decreased or unchanged for others. There were dramatic decreases in "sit idle" and "watching other calmly" while "sit tense and orient" categories sharply increased. The average distance between an animal receiving amphetamine and the other colony members did not increase as we had expected. When we looked at the individual relationships, it became evident that the amphetamine-treated animal

maintained closer contact with one individual, while moving further away or having less contact with others in the group. In each case we examined, the increased contact was directed towards that member of the colony with whom the test animal, during baseline period, spent the most time in affiliative social behaviors as grooming and huddling. The most dramatic result, however, was the effect of amphetamine on agonistic encounters. Agonistic responses dramatically increased during drug period ($P < 0.01$). The dominant animals of a colony increased their threatening during drug periods. Strikingly, the frequency of submissive responses by other animals did not increase accordingly. Subordinate members of the group did not increase their threatening behaviors when on the drug, but did significantly increase their submissive responses. However, the number of threats or approaches by the dominant animals did not increase. It is clear from these results that amphetamine administration increased the frequency of agonistic behavior in the treated animals. Furthermore, the type of agonistic behavior was dependent on, and appropriate to, the normal social position of the individual animal within the colony.

β-Endorphin and Other 31K Fragments: Pituitary Brain Systems

A series of studies were undertaken regarding the morphine-like peptides in the brain and pituitary. With the ONR support we were the first to show that this system could be changed by stress. Our efforts in this contract focused on the study of β-lipotropin (β-LPH) and β-endorphin (β-END) in pituitary and brain. An extensive series of studies were conducted, summarizing: we carried out immunocytochemical studies confirming the existence of the 31K precursor in two pituitary systems (anterior and intermediate lobes) with findings which strongly suggested the same synthetic route in the hypothalamic β-END neurons. We measured β-END immunoreactivity in human and rat blood and derived some hypotheses as to the regulation of

β-END in intermediate vs. anterior lobes of pituitary. We attempted to examine the potential role of β-END as a putative transmitter in brain, and obtained evidence of release of endorphin-like material in human CSF. Finally, we tested treatments were ACTH or β-MSH (both 31K fragments) were altered, and tested the effects of such treatments on brain and pituitary β-END. These investigations were part of our search for useful models for studying the physiological functions of β-END and ACTH. They were extended in exciting directions by our subsequent ONR support through SRO-001.

Enkephalin and Endorphin: Catecholamine Interactions

In this work we performed light microscopic studies of some of the interactions among peptide systems with the noradrenergic cells of the locus coeruleus and the thalamic noradrenergic bundle; and between noradrenergic fibers and the β-END/ACTH cells in hypothalamus. The results of the single-section enkephalin/noradrenergic studies in the locus coeruleus demonstrate that enkephalin fibers are found surrounding the noradrenergic cells and often between them. A serial-section study of the locus coeruleus with β-END antiserum and antiserum specific for the noradrenergic system showed there are many β-END fibers associated with the noradrenergic fiber bundle and surrounding the locus coeruleus cells. In other sections, prepared with both antisera, an occasional β-END fiber was seen coursing through the noradrenergic cell group. In serial sections, of the periventricular thalamus, the ascending noradrenergic bundle and descending β-END bundle appear to be intimately interwoven. Finally, in hypothalamic sections, the β-END cell group was found in the midst of a heavy field of noradrenergic fibers. It appears that β-END/ACTH cells may have noradrenergic inputs. These light microscopic studies tend to support several types of interaction between the noradrenergic system and the opiate peptides. For example, there may be enkephalin-noradrenalin interactions throughout the ascending

noradrenergic system. It is probably that such an interaction would be on a regional basis as enkephalin cells and fibers appear to be limited in their projection. On the other hand, the β-END/ACTH system seems to have the potential for massive interactions with the locus system through its rostral extent. From this preliminary, low resolution work one cannot draw conclusions about direct synaptic connections, yet it seems reasonable to hypothesize that the noradrenergic system may have substantial interactions with both the enkephalin and β-END/ACTH neuronal systems. Such interactions are of great interest in light of the findings from this laboratory, supported by ONR, that both the brain catecholamine and the brain endorphin systems are important in stress.

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